--46. A process for obtaining a mature protein heterologous to yeast as a product of yeast expression, which process comprises:

(a) culturing a yeast organism comprising an expression vehicle comprising a DNA sequence encoding an Arg C-terminal pre-pro peptide of yeast alpha factor operably connected in translation reading frame without intervening Glu (or Asp)-Ala dipeptide repeats to a DNA sequence encoding a mature protein heterologous to the yeast organism, wherein DNA encoding all of the Glu (or Asp)-Ala dipeptide repeats has been deleted from the pre-pro peptide of the yeast alpha factor DNA; and

(b) recovering mature protein from the culture.--

REMARKS

Claims 2-5, 7-8, 18-23 and 26-46 are presented herein for examination. Reconsideration of the outstanding objections and rejections is respectfully requested for the reasons that follow.

Amendments

The specification has been amended to correct typographical errors, to update the status of pending U.S. applications, to change "pBI" to "pB1" on page 22, line 3 to conform with the proper notation in the referenced application (see Fig. 17 of the enclosed copy of U.S. 4,775,622 into which US 438,236 matured, wherein the designation "pB1" is set forth in the circle drawing in the top right corner), and to insert text from two abandoned patent applications into various places of the specification that was incorporated by reference on pages 21 and 22 of the instant specification.

Specifically, the specification has been amended on pages 8, 21, 22, and 32 to insert selected disclosures of U.S. Ser. Nos. 06/438,128 and 06/452,227, both abandoned, which were incorporated by reference, together with the attendant bibliography and drawings. In the attendant bibliography and drawings, the citations and figures are re-numbered to follow sequentially the citation and figure numbers respectively given in the original

specification. This amendment is made to address the objection on page 4 of the Office Action.

A Declaration by the undersigned attorney is enclosed stating that the material from U.S. Ser. No. 06/438,128 that is inserted by amendment into pages 8, 21, and 32 of the above-identified application in this Amendment and the insertion of Figures 13, 14, 15A, 15B, and 16 into the above-identified application consist of the same material incorporated by reference in the above-identified referencing application, with the exceptions given in paragraph 2 of the Declaration. It is also stated that the material from U.S. Ser. No. 06/452,227 that is being inserted by this Amendment into pages 8, 22, and 32 and the insertion of Figure 17 into the above-identified application consist of the same material incorporated by reference in the above-identified referencing application, with the exceptions given in paragraph 3 of the Declaration.

Claims 1, 6, 9-17, and 24-25 are canceled without prejudice to file a continuation application directed thereto. Claims 2-4 and 7-8 have been amended to address the section 112, second paragraph, rejection as further detailed below. Claims 2-4 have their multiple steps lettered for clarity in reading and have their preambles and/or recovery steps specifying "mature" protein as set forth in the transformation step of the claims. Further, claim 7 is amended to incorporate the subject matter of now-canceled claim 6 on which it depends. Claims 7-8 contain language that characterizes the mature protein as being in discrete form and unaccompanied by substantial artifact of expression, as supported, for example, on page 6, lines 6-22 and as suggested by the Examiner on page 9 of the Office Action.

Further, claims 2-4 and 7-8 have been amended to clarify the nature of the alpha factor pre-pro sequence that is used herein. The pre-pro sequence set forth in these claims terminates at Arg rather than at one of the Glu/Asp-Ala sites and the pre-pro peptide has no intervening Glu (or Asp)-Ala dipeptide repeats. The basis for this language is found, e.g., on page 26, line 15 and in Fig.

11, which disclose preparing a deletion mutant in which the nucleotide sequence ending with Arg is linked directly to DNA encoding the N-terminus of alpha interferon by deletion of the dipeptide repeats formerly located upstream from the first alpha factor peptide plus some extraneous DNA located N-terminal to the alpha interferon gene. Note that the starting plasmid for this deletion contained only the first "89 amino acids of the α-factor `pre-pro' protein." Reference to Fig. 3 shows that all of the spacers and attendant α-factor sequences downstream from the first spacer were deleted in this construction. Therefore, the specification provides unambiguous support for these amendments to the claims, i.e., the first spacer was deleted by the mutagenesis and all the others had been deleted in making the starting construction subject to mutagenesis.

Claim 5 is amended to clarify that the DNA sequence encoding the pre-pro peptide is under the control of the promoter. Claims 18 and 19 are re-written to cover only one species, and new claims 26-31 cover each of the other species originally set forth in claims 18 and 19. Claims 18 and 19 are further revised to clarify the language regarding the heterologous protein. Claims 22 and 23 are revised to specify that the yeast organisms comprise the expression vehicles, as supported, for example, on page 2, lines 28-29 of the specification.

New claims 32-38 cover DNA molecules *per se*, as supported by the original claims and the amendments being made to them, which recite DNA sequences. Claim 32 is supported, e.g., by claim 2, claim 33 is supported, e.g., by claim 5, claim 34 is supported, e.g., by claim 10, and claims 35-38 are supported, e.g., by claim 9. New claim 39 corresponds exactly to claim 18 pending in the parent application. New claims 40-42 parrot claims 2-4 but do not require a transformation step. New claims 43-45 find support, e.g., in claim 5. New claim 46 presents claim 39 as an independent claim, but uses the language of claim 40 rather than that of claim 2 (no transformation step).

Interference

It is noted that the parent application is involved in an interference (No. 102,728; Brake *et al.* v. Singh). The final briefs were just recently submitted to the Board of Interferences and Appeals. Since the interference is not resolved and involves claims that may overlap with claims in the instant application, applicant believes that MPEP §709.01 applies and intends to file a Petition for Suspension to suspend prosecution of this application until the interference is finally resolved.

Election/Restriction Requirement

Restriction is required under 35 USC §121 to Group I (claims 1-11 and 16-25) and Group II (Claims 12-15). Applicant affirms the election of Group I made on January 5, 1996 and cancels claims 12-15 as drawn to a non-elected invention.

Drawings

Applicant will file formal drawings upon indication of allowable subject matter.

First Objection/Rejection under 35 USC §112, first paragraph

The specification is objected to, and claims 9-10, 17-21, and 24-25 are rejected under 35 USC §112, first paragraph, for allegedly failing to provide an adequate written description of the invention. The Examiner urges that the skilled artisan would be required to engage in excessive experimentation involving inventive activity in order to clone and characterize the insulin-like growth factor (IGF) gene to construct the expression vehicle claimed or use the expression vehicle to produce the protein by the claimed methods. As to vehicles for bovine interferon and rennin, the Examiner contends that the description on pages 21-22 refers to plasmids disclosed in patent applications as the source of the DNA, which information was not available to the public at the time the invention was made. The Examiner's position is that no DNA sequence information is provided for any of these genes nor the identity of the expression vectors pertaining thereto; hence, the

description of cells containing them and methods of using them to produce the corresponding proteins is also inadequate.

Claims 9-10, 17, and 24-25 have been canceled. As to the remaining claims, with respect to IGF-I and IGF-II, enclosed is a copy of the poster presented by Mullenbach *et al.* at the 74th Annual Meeting of the American Society of Biological Chemists (ASBC) on June 5-9, 1983, which is before the effective filing date of the instant application, i.e., before the filing date of the grandparent of the present application (June 20, 1983). (The abstract for this poster was published earlier on May 1, 1983 as Mullenbach *et al.*, Fed. Proc. Abstract 42: 1832 (1983), copy enclosed.) The poster indicates that the genes were able to be assembled in a single pool from their oligomeric components and each was expressed and secreted in yeast. The sequences used for the yeast expression are provided. (It does not describe or suggest bacterial expression of IGF-I or IGF-II.)

As to bovine interferon and rennin, while applicant does not necessarily agree with the Office's position, to expedite prosecution, the specification has been amended in various locations to incorporate by reference selected disclosures of U.S. Ser. Nos. 6/438,128 and 06/452,227 to which the specification refers on pages 21-22.

In view of the amendments to the specification, the above discussion, and the claim cancellations, applicant respectfully requests reconsideration and withdrawal of the objection and rejection of claims 9-10, 17-21, and 24-25 under 35 USC §112, first paragraph.

Second Rejection under 35 USC §112, first paragraph

Claims 9 and 24 are rejected under 35 USC §112, first paragraph, as the disclosure is allegedly enabling only for claims limited to human interferon alpha 1.

Since claims 9 and 24 are now canceled, applicant respectfully requests reconsideration and withdrawal of this rejection.

Third Rejection under 35 USC §112, first paragraph

Claims 2-4, 7-8, 16, 18-19, and 22-23 are rejected under 35 USC §112, first paragraph, as the disclosure is considered enabling only for claims to a yeast organism containing an expression vehicle comprised of DNA encoding the first 85 amino acids of yeast alpha mating factor pre-sequence ending with arginine operably connected in translation reading frame to DNA encoding the mature human interferon alpha 1.

First, the Examiner urges that the specification is unclear on what constitutes the pre-sequence, pro-sequence, or pre-pro peptide of alpha factor. Claim 16 is canceled. Claims 2-4 and 7-8, upon which all the other rejected claims depend, have been amended to indicate that the pre-pro sequence is an Arg C-terminal sequence and further that the sequence has no intervening Glu (or Asp)-Ala dipeptide repeats. Hence, the sequence of the alpha factor peptide positioned N-terminal to the gene for the heterologous mature protein is clearly defined.

The Examiner also states that the "protein" recited in claims 2-4, 7-8, 18-19, and 22-23 that is secreted or recovered has been assumed to be mature protein. Claims 2-4 now reflect clearly in their respective preambles and/or recovery steps that the protein is mature. Claims 7-8 already specified that the protein is mature, and claims 18-19 and 22-23 are dependent on claims 7 and 8.

The Examiner indicates that claims drawn to expression vehicles and yeast organisms transformed with the expression vehicles are included in this rejection as the specification allegedly only teaches using these products for producing the heterologous proteins encoded by the expression vehicles "in discrete form unaccompanied by any substantial peptide presequence or other artifact of expression, as a product of yeast expression, processing and secretion," referring to the specification at page 6, lines 6-22. Accordingly, claims 7 and 8, upon which claims 18 and 19 depend, directed to the expression vehicles, are amended to characterize the mature protein using this language. The yeast

organism claims 22 and 23 also depend from claims 7 and 8, respectively.

The Examiner moreover alleges that the specification teaches that the processing steps are unpredictably different in yeast than in mammalian systems and that secretory processes in yeast were not fully understood before the effective filing date. It is further contended that the specification provides only a single working example of a yeast transformed with an expression vehicle which produces a mature heterologous protein, at pages 25-27, wherein the protein is initially expressed as a fusion with an N-terminal pre-sequence of the first 85 amino acids ending with Arg of yeast alpha mating factor pre-pro protein fused to the mature interferon polypeptide.

The Examiner states that using an 89-amino-acid pre-sequence having two Glu-Ala repeats results in N-terminal amino acids not present in the native mature proteins. However, the claims have now been amended to recite that the pre-pro sequence is free of intervening Glu (or Asp)-Ala dipeptide repeats, thereby eliminating the possibility of extraneous N-terminal sequence objected to by the Examiner.

The Examiner further contends that only trace amounts of rennin and tissue plasminogen activator were secreted and they were not analyzed with respect to complete or proper processing. The specification is enabling for any protein, since even trace amounts are sufficient because they show that more than one species in the protein genus encompassed by the claims was detectably operable. Even though there is a single working example, that example without intervening dipeptide repeats shows that the invention works. The citation by the Office of Szebo *et al.*, J. Biol. Chem., 261: 5858-5865 (1986) does not alter this conclusion, as 50% of the protein produced from the construct lacking the repeats was processed. The fact that work by others cited in Szebo *et al.* indicated that gene fusion with the Glu-Ala repeats gave incompletely processed N-

termini further supports the claims as now amended, which recite that the peptide does not contain the repeats.

In view of the amendments to the claims, applicant believes that once the claimed invention was made known through the specification, one skilled in the art would have been able, without undue experimentation, to obtain secretion of "mature" protein using an alpha-factor pre-pro sequence as now defined in the claims. The passages in the above-identified specification referring to unpredictability in the art that are cited by the Examiner characterized the art before the invention was made known. Szebo *et al.* does not contradict these statements in the specification, since after the filing date Szebo *et al.* still obtained properly processed protein using constructs lacking the dipeptide repeats.

Hence, applicant respectfully requests reconsideration and withdrawal of the rejection of claims 2-4, 7-8, 16, 18-19, and 22-23 under 35 USC §112, first paragraph.

Rejection under 35 USC §112, second paragraph

Claims 1-11 and 16-25 are rejected under 35 USC §112, second paragraph, for allegedly being indefinite in pointing out the subject matter claimed.

Claims 1-11 and 18-25 are deemed indefinite for the recitation of "the DNA sequence" in claims 1-6 and 8, which allegedly lacks antecedent basis. Claims 1 and 6 are canceled; the remaining independent claims have been amended to obviate this rejection.

Claims 1, 6-7, 9-11, 18, 2,[1] and 22 are deemed indefinite for recitation of "the promoter" in claims 1 and 6, which allegedly lack antecedent basis. Claims 1, 6, and 9-11 are canceled, and amended claim 7, which contains the recitations of claim 6, and

[1] Applicant assumes for purposes of this rejection that claim 2 is a typographical error and should be claim 20. Claim 2 does not use the word "promoter," whereas claim 20 depends on claim 7, which does use the word "promoter."

upon which all the other rejected claims depend, has been amended to clarify the promoter being recited.

Claims 2-5, 7-8, and 18-23 are deemed indefinite for reciting "substantially the pre-pro peptide of yeast alpha factor" in claims 2-4 and 7-8. Claims 2-4 and 7-8 upon which all the other rejected claims depend are amended to define the pre-pro peptide as having a carboxy-terminal end terminating in Arg. This eliminates the objection to the terms "the pre-pro peptide" and "substantially."

Claims 16-17 are rejected as being allegedly indefinite for reciting "capable of producing" in claim 16. Claims 16 and 17 have now been canceled, thereby mooting this rejection.

In view of the amendments to and cancellation of the claims, applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 USC §112, second paragraph.

First Rejection under 35 USC §102(e)

Claims 1-8, 11, 16, and 22-23 are rejected under 35 USC §102(e) as being anticipated by Kurjan *et al.* (U.S. 4,546,082). Claims 1, 6, 11, and 16 have been canceled. The remaining independent claims upon which all other rejected claims depend have been amended to recite an Arg C-terminal pre-pro peptide connected to the gene for the heterologous protein without intervening Glu (or Asp)-Ala dipeptide repeats, a feature not taught by Kurjan *et al.*

In each construction taught by Kurjan *et al.*, the first HindIII site shown in Figure 1A of Kurjan *et al.* has been cut and filled in to give a blunt-ended segment, RH2, which terminates in the Glu-Ala spacer peptide (col. 5, lines 44-48; col. 10, line 66 to col. 11, line 2). RH2 has the structure:

alpha-factor leader-LysArg-GluAlaGluAla.

All constructs taught in Kurjan *et al.* are based on this RH2 segment (col. 11, line 39; col. 12, line 18) and, therefore,

inherently have the Glu-Ala spacer that is specifically excluded from the instant claims as amended. When discussing the invention generically, Kurjan *et al.* also teach the cutting of alpha-factor at the HindIII site (at positions 263-268) for insertion of the heterologous coding sequence (col. 5, lines 44-46). Figure 1A of Kurjan *et al.* distinctly shows that this HindIII site is at the end of spacer 1 and its use necessarily results in the sequence -Glu-Ala-Glu-Ala- appearing between the N-terminus of the desired protein and the -Lys-Arg- cleavage site of the alpha-factor leader, contrary to the constructions now instantly claimed.

Since Kurjan *et al.* only teaches constructions employing the complete spacer sequence (including the Glu-Ala codons) in fragment RH2, the present claims are not anticipated by Kurjan *et al.*

In view of the above discussion and claim amendments and cancellations, applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 USC §102(e) over Kurjan *et al.*

Second Rejection under 35 USC §102(e)

Claims 1-8, 11, 16, and 22-23 are rejected under 35 USC §102(e) as being anticipated by Brake *et al.* (U.S. 4,914,026). Claims 1, 6, 11, and 16 are canceled, so their rejection is moot. With respect to the remaining claims, claims 2-4, and 7-8, upon which all other rejected claims depend, have been amended to recite that the pre-pro alpha-factor peptide sequences are without intervening Glu (or Asp)-Ala dipeptide repeats. There is no teaching in Brake *et al.* of this feature of the claimed invention. The passages in the specification of Brake *et al.* cited by the Examiner, especially cols. 3, 6, and 8 with the most detail, do not provide this critical information and thus Brake *et al.* does not anticipate the claimed invention.

In view of the above discussion and the claim amendments and cancellations, applicant respectfully requests reconsideration and

withdrawal of the rejection of the claims under 35 USC §102(e) over Brake *et al.*

Rejection under 35 USC §103

Claims 9, 18-19 and 24 are rejected under 35 USC §103 as being unpatentable over Kurjan *et al.*, *supra*, in view of Goeddel *et al.* (U.S. 4,762,791). Claims 9 and 24 are canceled, so the rejection with respect to these claims is moot.

As to the remaining claims 18-19, the key issue is whether one of ordinary skill in the art would have been able to predict reasonably, at the effective filing date when applicant filed the grandparent application, that the alpha-factor processing and secretion system would be able to process and secrete heterologous proteins fused to an Arg C-terminal pre-pro peptide of the alpha-factor precursor from which the so-called "spacer" sequence has been deleted, such that the resulting heterologous protein would be processed perfectly from the alpha-factor preprotein fusion without any residual extraneous N-terminal polypeptide.

Applicant originally had constructed vectors in which the DNA encoding the mature heterologous protein had been ligated to the codon encoding Ala_{89} of pre-pro alpha-factor (Fig. 7). This residue is located immediately proximal to the first residue of the first alpha-factor monomer. Theoretically, this would be the most logical site for the insertion of heterologous DNA because this is the ultimate processing site for mature alpha-factor. However, applicant's actual experimental studies revealed a surprising result. While yeast could cleave fusions of the alpha-factor pre-pro sequence after the pre-pro LysArg dipeptide in the "spacer" regions of the alpha factor precursor with reasonably high fidelity, yeast were not particularly adept at removing the spacer X-Ala dipeptides from the N-terminus of the heterologous protein.

As shown in the specification at page 25, for example, 63% of the pre-pro alpha-factor bovine interferon fusion was processed at the Lys-Arg site, but only 13% had the first Glu-Ala dipeptide

removed. Another 24% of the secreted interferon was cleaved at a Glu residue present in the fusion as a result of translation of the adaptor DNA used to ligate the alpha-factor peptide to the interferon gene. For the reasons set forth in the specification at page 25, lines 28-34, applicant decided that it would be "preferable to produce and secrete into the growth medium proteins that are identical to the proteins from the natural sources." This was accomplished by deleting the nucleotides encoding the dipeptides of the "spacer" molecule so that processing would need to take place only after the Lys-Arg. Upon transformation and culturing, the major sequence of the secreted protein was determined to have the first eight N-terminal amino acids of the mature protein (specification page 27, lines 14-15).

This result was particularly surprising in view of Kurjan *et al.* As discussed above, Kurjan *et al.* describe a method for secreting heterologous polypeptides from yeast using the alpha factor gene. According to Kurjan *et al.*,

> by deleting the alpha-factor coding sequences in the alpha-factor precursor and by inserting other useful proteins between the spacer coding regions, or by fusing to these regions, the resultant fusion polypeptide is not only be (sic) expressed, but also may be secreted from the yeast cell and processed by the yeast proteolytic processing enzymes... (col. 3, lines 24-31)

Examples 9a, 9b, and 9c of Kurjan *et al.* describe prophetic methods for the secretion of heterologous peptides from yeast using the alpha-factor signal. The constructions used in Examples 9a and 9b are shown in Figs. 3 and 4, respectively. These consist of pre-pro alpha-factor-spacer 1-preprosomatostatin and pre-pro alpha-factor-spacer 1-preACTH. In both cases, Kurjan *et al.* hypothesize that yeast will process and secrete the alpha factor pre-pro segment in the ordinary fashion and <u>then</u> cleave at the Lys-Arg site of the <u>heterologous</u> preprotein (col. 11, lines 25-29 and col. 11, lines 57-61). Similarly, in Example 9c Kurjan *et al.* go to the

special effort of actually introducing a Lys-Arg dipeptide after fragment RH2 (the same fragment used in Examples 9a or 9b which contains the alpha-factor pre-pro sequence and first spacer sequence as described above).

Thus, rather than attempting to employ the Lys-Arg processing site of the pre-pro sequence, Kurjan *et al.* teach introducing an exogenous Lys-Arg site. The reason for this burdensome redundancy is apparent from the Kurjan *et al.* statement that:

> [T]hese spacer peptides are presumed to contain the recognition regions which determine how the precursor is proteolytically processed. (col. 4, lines 25-28)

The reason for this redundancy is also apparent from the statement of Kurjan *et al.* that use of the pre-pro sequence terminating in the HindIII site at 263-268:

> [leaves] intact the first spacer peptide which may be the recognition signal for proteolytic processing by yeast enzymes. In such a case the yeast cell may secrete the mature form of the polypeptide of interest, thereby obviating the necessity of processing a fusion product. (col. 5, lines 45-51)

Kurjan *et al.* suggest in col. 6, lines 18-23 that this construction results in the secretion of a protein without any additional amino acids in its N-terminus. This is incorrect. Enclosed herewith is a copy of a paper published after the filing date of the grandparent to this application, Brake *et al.*, Proc. Natl. Acad. Sci. USA, 81: 4642-4646 (1984), which is reference 17 of the Information Disclosure Statement mailed January 25, 1996 in connection with this application, so is presumably of record. This paper presents data regarding the expression constructions shown in Figures 1 and 2 of U.S. Pat. No. 4,870,008 (ref. 4 of the January 25, 1996 Information Disclosure Statement; copy enclosed), which is in the present interference Brake *et al.* v. Singh because it claims the same invention.

The authors of the Brake *et al.* paper attempted several constructions: one with the native spacer (Lys-Arg-Glu-Ala-Glu-Ala), one in which additional codons for a Lys-Arg cleavage site were inserted between the spacer and the heterologous coding sequence, and several in which the Glu-Ala codons were removed between the Lys-Arg cleavage site and the heterologous protein coding sequence. In all cases where the Glu-Ala dipeptides were expressed, incomplete processing of the pre-pro protein occurred, resulting in additional amino acids at the N-terminus of the desired protein. See Table 1 of the Brake *et al.* article.

Thus, ironically, leaving the spacer peptide in place produces, in fact, the opposite result from that contemplated by Kurjan *et al.*; the spacer peptide or fragments thereof are not efficiently removed by yeast from the amino terminus of the heterologous polypeptide. Use of the spacer sequence thus ensures an improper amino terminus. Accordingly, in advocating the use of the spacer sequences, Kurjan *et al.* clearly would have taught away from applicant's amended claims, which call for the use of the Arg C-terminal pre-pro alpha factor peptide from which specified dipeptide repeats are deleted. Applicant's amended claims also distinguish from Kurjan *et al.* in providing that the deletion-modified Arg C-terminal pre-pro sequence is linked to DNA encoding a mature heterologous protein; Kurjan *et al.* use DNA encoding heterologous preproteins or, as in Example 9c, modified proteins having an intermediate artificial processing site.

Goeddel *et al.* does not compensate for or supply the deficiencies of Kurjan *et al.* It does not teach or suggest use of Arg C-terminal pre-pro sequences of alpha-factor connected in translation reading frame, without intervening selected dipeptide repeats, to the gene encoding the foreign protein (human gamma-interferon in the case of Goeddel *et al.*), as now embodied in claims 7 and 8 upon which rejected claims 18 and 19 ultimately

depend. Goeddel *et al.* simply teaches the cloning and nucleotide sequence of pre- and mature human interferon gamma.

Unexpectedly, therefore, applicant has found that the use of the alpha factor spacer segment is deleterious to the preparation of mature heterologous proteins, and that, surprisingly, it can be deleted without misdirecting the heterologous protein within the yeast secretory mechanism or exerting any toxic effect on the cells. Since Kurjan *et al.* at no point recognized the consequences or desirability of eliminating the Glu-Ala region from the spacer, the present claims could not have been obvious from Kurjan *et al.*, either alone or in combination with Goeddel *et al.* Indeed, Kurjan *et al.* suggests, incorrectly, that one can obtain properly processed proteins employing the constructions disclosed therein.

While one skilled in the art would not have reasonably expected applicant's invention to be successful prior to the effective filing date, now that applicant has demonstrated the utility of the system, the use of the partially deleted alpha-factor pre-pro sequence for secretion of heterologous proteins from yeast is fully enabled.

In view of the above discussion and the claim amendments and cancellations, applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 USC §103.

Provisional Double Patenting Rejection

Claims 2-5, 7-8, 16, 18-19, and 22-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 19-21 of copending application Serial No. 07/552,719, the parent of this application. Since the parent application is still pending and this rejection is provisional, applicant asks that this issue be deferred until final resolution of the interference. While the parent application is involved in an interference, applicant is unable to prosecute the claims therein, but once the interference

is finally resolved, applicant can take the appropriate action to handle this issue.

If the Examiner has any questions, he should feel free to contact the undersigned attorney at the number indicated below.

Respectfully submitted,

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